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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/732,411	12/07/2000	Samy Ashkar	CMZ-124CP	1508

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 02/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/732,411	ASHKAR, SAMY	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7,16 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7,16 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 12/22/05, is acknowledged.

2. Claims 1, 3-5, 7, 16 and 18 are pending and under examination as they read on a method of inhibiting adhesion of a target cell to a substrate comprising providding the target cell with the adhesion modulatory peptided associated substrate SEQ ID NO:15 (inhibits VLA-4/VCAM interaction) such that adhesion of the target cell to the substrate is inhibited wherein the target cell is endothelial cells, neutrophil and macrophage and wherein the substrate is titanium, a polyvinyl surface, a gel, collagen, hyaluronic acid and PGA.

3. In order to facilitate the prosecution of this application, Applicant is requested to cancel all non-elected embodiments from the claims.

Applicant points to US 37 CFR 1.146, which states that in the first action on an application containing a generic claim to a generic invention (genus) and claims to more than one patentably distinct species embraced thereby, the examiner may require the applicant in the reply to that action to elect a species of his or her invention to which his or her claim will be restricted if no claim to the genus is found to be allowable. Applicant contends that the requirement for restriction is for search purposes. Applicant submits that no art having been found which discloses the elected species SEQ ID NO: 15, the examination of the remaining species shoul now be conducted.

However, the Examiner would like to draw Applicant's attention the Office Action mailed on 2/05/02, wherein no sequence i.e., SEQ ID NO species election was set forth in said office Action, but rather separate groups invention election base on the claimed sequences because the specification indicates that each individual peptide has different function and widely vary in their size and composition.

4. In view of the amendment filed on 12/22/05, only the following rejection are remained.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 3-5, 16 and 18 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "glycosaminoglycan, fibrinogen, collagen, vitronectin, thrombospondin, osteopontin, bone sialoprotein !, von Willebrand's factor" claimed in claim 1, lines 2-3 represents a departure from the specification and the claims as originally filed.

Applicant's amendment filed 1/07/05 points to the specification at pages 5-8 and 19-20 for support for the newly added limitations "glycosaminoglycan, fibrinogen, collagen, vitronectin, thrombospondin, osteopontin, bone sialoprotein , von Willebrand's factor" as claimed in claim 1. However, the specification does not provide a clear support of such limitation with SEQ ID NO: 15. The Examiner notes that the specification on page 10, table II lists claimed VLEP of SEQ ID NO: 15 functions to inhibit VLA-4/VCAM interaction. Further, the specification on page 6, lines 6-17, discloses that alpha4/beta1 (VLA-4) is a receptor for fibronectin containing the CS-1 region which is situated within the IIICS region and VCAM-1. The Examiner was not able to find a clear support that claimed SEQ ID NO:15 inhibits binding of a cell to a "glycosaminoglycan, fibrinogen, collagen, vitronectin, thrombospondin, osteopontin, bone sialoprotein , von Willebrand's factor". The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

Applicant's arguments, filed 12/22/05, have been fully considered, but have not been found convincing.

Applicant argues that while the Examiner's position that the exact phrase is not associated with SEQ ID NO: 15 is without merit. Claim 1 is not limited to SEQ ID NO: 15 but to a class of peptides, of which SEQ ID NO: 15 is one.

However, claim 1 still reads on a method of inhibiting binding of a cell to an integrin, glycosminoglycan, fibrinogen, fibronectin, collagen, vitronectin, thrombospondin, osteropontin, bone sialoprotein 1, von Willebrand's factor or vascular adhesion molecule with SEQ ID NO: 15. Besides the inhibition of VLA-4/VCAM interaction, the specification fails to disclose association of SEQ ID NO:15 with all recited compoents.

7. Claims 1, 3-5, 16 and 18 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting binding of a neutrophil or macrophage cell to a fibronectin or to endothelial cells *in vitro*, with the adhesion peptide consisting of SEQ ID NO: 15, does not reasonably provide **enablement** for a method for inhibiting binding of any cell to any integrin or glycosaminoglycan, fibrinogen, collagen, vitronectin, thrombospondin, osteopontin, bone sialoprotein I, Von Willebrand's factor, or vascular adhesion molecule comprising providing the cell with a peptide molecule comprising a a peptide having a molecule weight between 100 and 2500 Daltons and consisting of SEQ ID NO:15 in claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action mailed 9/29/05.

Applicant's arguments, filed 12/22/05, have been fully considered, but have not been found convincing.

Applicant submits that the specification on page 1 lines 15-33 discusses the proteins involved in cell adhesion, which are well known in the art. Further, the specification on 14-17 discloses how to make the adhesion modulatory peptides and on page 10-11(table II), a method of how to use the claimed peptides to modulate cell adhesion. The specification on page 10 (table II) disclose that SEQ ID NO: 15 can be use to inhibit the interaction between the integrin VLA-4 and it ligand VCAM interaction. Applicant draws the Examiner's attention to Yabkowitz et al Isobe et al and Bayless et al for support that VLA-4 has other ligands other that fibronectin and VCAM. Further Applicant point that the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and is already available to the public. Applicant points to the specification on page 9, lines 1-9 which sets forth the relative ease with which one skilled in the art would determine an adhesion receptor pattern for a particular cell type. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. Applicant alleged that the examiner has only provided speculation and unsupported arguments for why the specification is not enabling. It is well established that a specification is presumed to be enabling. A prima facie case of non-enablement can only be made upon a showing of evidence (not argument) of why one skilled in the art would not be able to make and use the claimed subject matter. Applicant submits that event assuming arguendo that the examiner has done so, applicant has rebutted this with reference to support not only in the specification but in the literature.

Regarding the issue that VLA-4 has other ligands other than fibronectin and VCAM, the Examiner notes that the specification discloses that SEQ ID NO: 15 inhibits VLA-4/VCAM interaction. The specification fails to provide evidence that claimed VLEP of SEQ ID NO: 15 is a signature motif that would inhibit the interaction between VLA-4 and any other ligands. Further, not all other ligands would have a consensus VLA-4-binding motif for SEQ ID NO: 15 to be one that fits all inhibition of VLA-4/ligands. For example, Bayless et al on page 1166, 1st col., 1 ¶ teaches that α4β1 integrin has been reported to bind the CS-1 and CS-5 alternatively spliced domains of fibronection as well as VCAM-1. Known binding sequences for the α4β1 integrin are LDV in the CS-1 region of fibronectin and QIDSPL in VCAM-1. Other identified recognition sites for α4β1 within fibronectin include IDAPS, REDV and RGD. Importantly, Bayless et al (page 1172, 1st col., 1¶) concludes that while the N-terminal domain of the OPN may facilitate leukocyte adhesion through α4β1, there is not LDV, IDS or EDV sequences within this domain which are known α4β1-bidning sites for either fibronectin or VCAM-1. Bayless et al concludes that the α4β1-binding site within OPN will be a novel binding site, possibly related to LDV or IDS, and further work will be necessary to identify this site. Similarly, Isobe et al identify a novel integrin-binding motif of 15-residue peptide designated T2-15 (DCQDHSFSIVIETVQ) residues numbered 395-409 of pp-vWF) promoted VLA-4 dependent cell adhesion (see abstract in particular). Finally, Yabkowitz et al fail to teach the

integrin-binding motif of thrombospondin that promotes T-cell adhesion via $\alpha 4\beta 1$. Therefore, VLEP of SEQ ID NO: 15 is not the pharmaceutical version of the "all for the price of one".

Regarding the issue that the specification on page 9, lines 1-9, set forth the relative ease which one skilled in the art would determine an adhesion receptor pattern for a particular cell type.

However, the instant fact pattern fails to indicate that a representative number of a receptor expression profile for any cell is disclosed. The artisan would not know the identity of a reasonable cell type falling within the scope of the instant claim and consequently would not have known how to use them. In order to satisfy 112, first paragraph, the specification has to teach how to make and use SEQ ID NO: 15 of the invention not how to identify the invention.

In contrast to applicant's continued assertions that the examiner has relied upon speculation and unsupported arguments for why the specification is not enabling; the examiner in the instant application has set forth an adequate explanation with supporting evidence to support the rejection under 112, first paragraph, based upon the Forman factors of record. After evidence or arguments is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument. It is noted that the references used in the Applicant's rebutted supports the Examiner's position.

8. Claims 1, 3-5, 16 and 18 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 9/29/05.

Applicant's arguments, filed 12/22/05, have been fully considered, but have not been found convincing.

Applicant asserts that he is in possession of the claimed subject matter at the time of filing. Applicant points to the specification on pages 14-17 describe how one can make the peptides to be used in inhibiting cell binding, the specification at page 9-10 discloses the amino acid composition of the peptide recited in the claim and a distinguishing characteristic for each. Applicant submits that the structural description of integrins, glycosaminoglycan or vascular adhesion molecules are well known in the art. Applicant points to the *Spectra-Physics, Inc. V. Coherent, Inc.* 827 F. 2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

However, the specification fails to describe integrins, glycosaminoglycan or vascular adhesion molecules that would be inhibited with the VLEP of claimed SEQ ID NO: 15, besides VLA-4/VCAM interaction. No such substances were made or shown to have activity. The specification's general discussion of making and identifying for substances constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written

description for the claimed substances. Putting the claimed methods into practice awaited someone actually discovering a necessary component of the invention. Without the substances called for in the methods, Applicant could no more be said to have possessed the *complete* claimed invention.

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

January 23, 2006

Maher Haddad

Maher Haddad, Ph.D.
Patent Examiner